Phenethylbiguanide in Diabetic Patients

Clinical and Metabolic Effects

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• **Phenethylbiguanide (DBI) was given to 70 unselected but not obese diabetic patients who were receiving restricted diabetic diets. The only side effects attributed to the drug were anorexia, nausea, vomiting and diarrhea in 28 patients. These symptoms subsided with reduction of dosage. No evidence of serious toxicity has been demonstrated in clinical and metabolic studies. In 27 of the 70 patients diabetes was controlled adequately with DBI alone, and more stable control was obtained in 11 labile diabetics who received DBI in combination with insulin.**

The mechanism of action is not definitely known.

A NEW nonsulfonylurea, hypoglycemic compound discovered recently by Ungar[1] has stimulated further the investigation of effective oral substitutes for insulin in the treatment of diabetes mellitus. This new synthetic drug, N'-betaphenethylformamidinyliminourea hydrochloride (hereafter referred to as DBI) has been reported as an active, potent, hypoglycemic agent, effective in certain animals[8,9,10] and in patients[2,3,6,7] with diabetes mellitus.

The purpose of the studies herein reported was to observe the effects of DBI in 70 diabetic patients. A definite diagnosis of diabetes mellitus had been established previously in all patients of this series. There was careful dietary regulation in each case and none were obese. Administration of insulin had been necessary for adequate control in 59 patients, and control of the 11 patients not taking insulin was unsatisfactory after periods of observation on a restricted diabetic diet alone.

Seventy known diabetic patients, including juveniles and patients with complications such as Kimmelstiel-Wilson's syndrome and osteomyelitis, were studied for periods of from seven days to sixteen months. Fifty-three of these patients were in hospital and 17 were observed as out-patients. Diets were constant and weighed. Before therapy was started these patients had the following studies: Electrocardiogram, blood cell counts, urinalysis, determination of protein-bound iodine, phenolsulfonphthalein test (intravenous), blood urea nitrogen, total cholesterol determination, Bromsulphalein, cephalin flocculation and thymol turbidity tests and determination of total serum bilirubin. During therapy these examinations were repeated at various intervals. Capillary blood glucose determinations, by the Somogyi-Nelson method, were made fasting or three hours after breakfast and lunch. Urine glucose was determined by the Benedict method, at 7:30 a.m., 11:00 a.m., 3:00 p.m. and 9:00 p.m., and 24-hour excretion of glucose was measured for each in-patient and for seven out-patients.

There were 34 males and 36 females in the series. The age range was from 6 to 84 years, the average 53 years. The duration of diabetes was from one year to 29 years, and the average was 10.6 years.

All patients were maintained on a restricted diabetic diet during the period of observation, and criteria for control established previously by Lambert and co-workers[4] were used to determine adequate control during observation. These criteria were as follows:

1. Three-hour postprandial "true" blood sugar levels* of less than 150 mg. per 100 cc.
2. Reasonable 24-hour urinary excretion of sugar (that is, less than 7 gm).
3. Prevention of ketosis.
4. Absence of symptomatic hypoglycemia.
5. Tolerance of drug without toxicity.

RESULTS AND REPORT OF CASES

Successful treatment on DBI alone has continued for 27 patients, and 11 patients have maintained more stable control on a combination of DBI and insulin. Administration of DBI was discontinued in 12 patients, even though they had adequate control, because of side effect. Two well regulated patients moved to areas where careful observation was not possible. In 18 patients there was no demonstrable blood sugar lowering effect.

Chart 1 demonstrates the effect in a 40-year-old man with diabetes of one year's duration. His weight was 145 pounds and he had not had adequate control on a restricted diabetic diet with 20 units of insulin daily. Insulin was discontinued for

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*"True" blood sugar level of 150 mg. per 100 cc. is equivalent to 180 mg. per cent Folin-Wu value of criteria previously established.

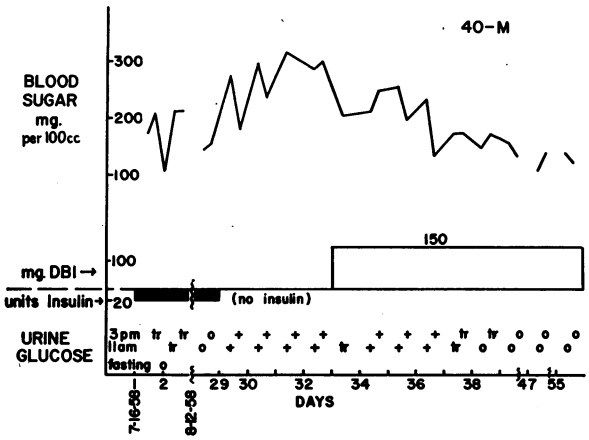


Chart 1.—Diabetic control with 150 mg. of DBI daily in a 40-year-old man after insulin was withdrawn for 4 days (tr. = trace).

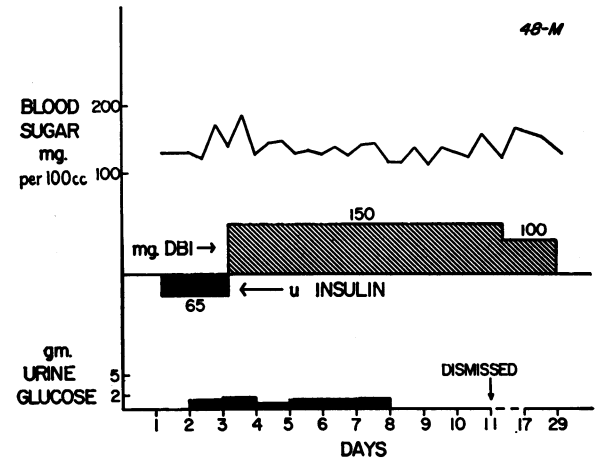


Chart 2.—Effect of DBI in adequate regulation of diabetes aggravated by osteomyelitis.

four days, with a resulting hyperglycemia and glycosuria, before the administration of DBI.

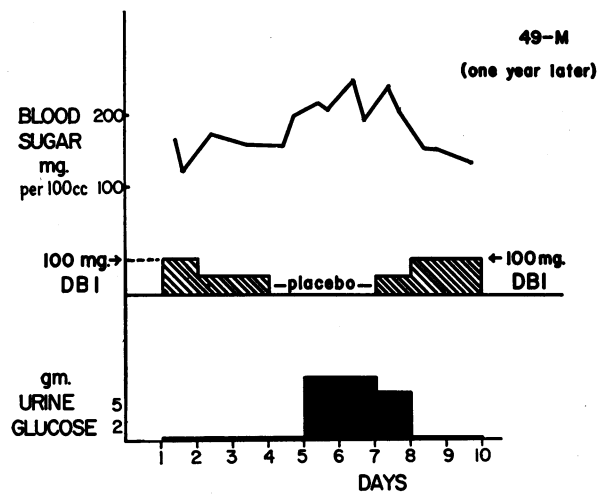
Chart 2 shows the control in a 48-year-old man with osteomyelitis of the right foot. In this patient diabetes was of seven years' duration and his weight was 153 pounds. He had required 65 units of insulin daily. Adequate control was obtained with 150 mg. of DBI daily, and eventually with 100 mg. After one year the osteomyelitis had subsided and in Chart 3 is shown the result of substituting a placebo for DBI: Hyperglycemia and glycosuria became evident and DBI was resumed.

Chart 4 shows the effect of DBI alone in a 14-year-old boy with known diabetes for one year. Nausea developed with the dose at 150 mg. per day, and DBI was discontinued after six days because of ketosis.

The response to combined therapy of insulin and DBI in a 50-year-old, brittle diabetic woman weighing 112 pounds is shown in Chart 5. Diabetes in this case was of 24 years' duration. She had been observed while receiving a constant, weighed diabetic diet plus insulin for three weeks before trial of combined DBI and insulin therapy. The diabetic condition has remained stabilized.

The patients in whom DBI alone gave adequate control of diabetes were 40 years of age or older, the range being from 40 to 73, with an average of 60.9 years. Daily insulin requirements of patients taking insulin in this group were 15 to 65 units and the mean was 28.5 units.

The average daily excretion of sugar for patients in whom diabetes was well controlled by insulin therapy was 2.6 gm; the range was from 0.6 to 6.5 gm. The average daily excretion when they were receiving DBI was 1.7 gm., and the range 0.6 gm. to 5.9 gm. Dosages of DBI varied. At first, adults were given 150 mg. and children 75 mg. in divided



3. Chart 3.—Demonstration of long term control of diabetic condition of same patient shown in Chart 2. Maintenance therapy with 100 mg. DBI daily for one year preceded placebo of 4 days.

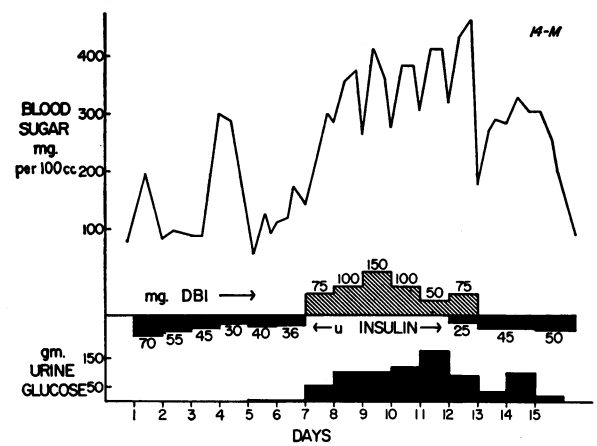


Chart 4.—Ineffectiveness of DBI alone in juvenile diabetic. No response in 14-year-old boy with dosage up to 150 mg. daily.

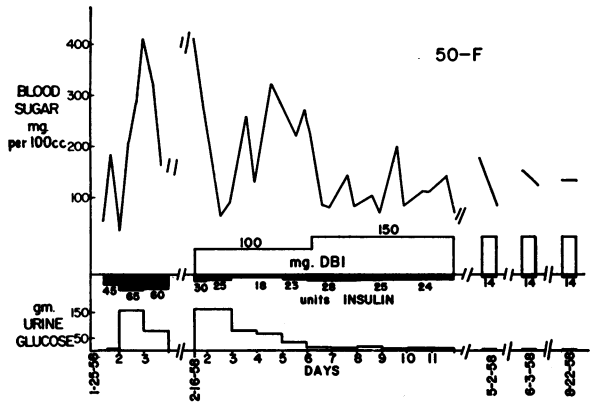


Chart 5.—Stabilizing effect of DBI in combination with insulin in adult labile diabetes.

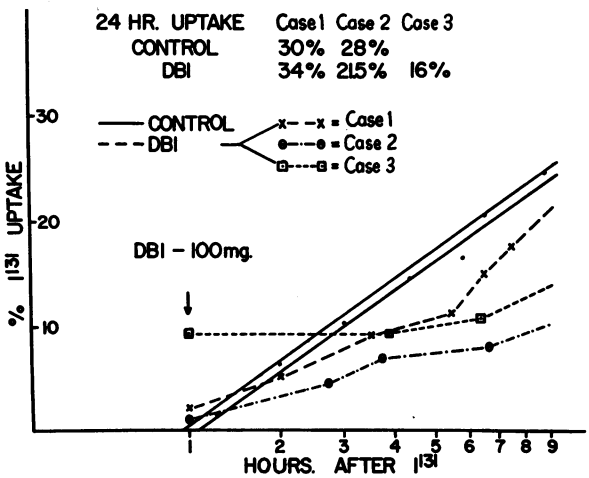


Chart 6.—Temporary effect of DBI in suppressing iodide uptake by the thyroid gland. The solid lines represent the control radioiodine uptake in these patients before the administration of a single dose of 100 mg. of DBI. The broken lines demonstrate the acute effect of DBI upon iodide accumulation by the thyroid in these three patients.

doses daily. Doses as high as 300 mg. were administered before nausea occurred. The patients who had adequate control while receiving DBI required 50 mg. to 225 mg. of the drug daily; the average was 114 mg.

No impairment of liver or kidney function was detected after the administration of DBI, and no changes were observed in repeated hematological studies.

Changes in electrocardiographic tracings of three patients were noted after long continued administration of this hypoglycemic agent, but it was not determined that these effects were due to DBI. There was no significant effect on the electrocardiograms of four patients who had hourly examinations after a single dose of 100 mg. of DBI. Six patients in whom serial determinations of radioactive iodine accumulation were carried out while they were receiving DBI, showed suggestions of moderate, intermittent reductions of iodide accumulation by the thyroid for four to five hours after a single dose of the drug. This effect in three of these patients is shown in Chart 6. The 24-hour I^{131} uptake of two patients was decidedly depressed after two weeks of treatment with the compound, but returned to normal range after four weeks without discontinuance of DBI therapy.

There were no significant changes in the 17 hydroxycorticosteroids in the urine of six patients after they had taken DBI for from two to four weeks.

Fasting control values for serum sodium, potassium, chloride, calcium, phosphorus, bicarbonate and lactic acid were determined for five patients after three days of constant weighed diets, and these determinations repeated after three days of DBI therapy on the same diet. Similar studies were done on 24-hour urine volumes. No appreciable effect on the balance of sodium, potassium, chloride or bicarbonate was noted. Blood lactic acid was elevated in one patient and minor changes in phosphorus balance occurred in three patients.

COMMENT

In the present series of 70 diabetic patients a restricted diabetic diet was maintained before therapy with DBI was begun. They had been observed while being treated by diet alone or diet plus insulin. In some instances, insulin had been discontinued before treatment with DBI and in others DBI was discontinued during treatment, with hyperglycemia and glycosuria resulting in either case.

There was adequate control with DBI alone in 27 patients. Ten of this group had anorexia, nausea, vomiting or diarrhea within the first one or two weeks of treatment. These symptoms disappeared with continuation of DBI in some cases, and with reduction of dosage temporarily in other instances. Thirty-seven of the 70 patients had side effects of this kind. In nine of these patients, either brittle adult or juvenile diabetics, these side effects were attributed to ketosis which was evident as early as 24 hours after DBI was first administered. The side effects experienced by the other 28 patients were attributed to irritation of the gastrointestinal tract or to some unknown cause. Whether the DBI tablets were given before, during or after meals made little difference so far as side effects were concerned, and antispasmodics or antacids taken before or after the drug did not ameliorate these unpleasant and annoying symptoms.

Nine of the patients in whom control of diabetes was obtained with DBI alone or in combination with insulin, who had side effects during the first weeks of therapy with DBI but were able to continue treatment, showed a temporary reduction in weight of

as much as two to seven pounds. By maintaining their required daily total caloric intake, all returned to their standard weight without discontinuance of DBI treatment.

There was a definite hypoglycemic action of DBI and evidence of adequate control in ten patients who discontinued the drug because of nausea and vomiting. Two juvenile and nine adult labile diabetic patients obtained better control with DBI combined with insulin than with insulin alone. Insulin dosages were reduced 50 per cent in some instances.

The suggestion of antithyroid activity of DBI demonstrated by the I^{131} accumulation gradients of six patients and depression of 24-hour I^{131} uptake in two patients cannot be explained adequately. Experimental data[1] points to peroxidase as probably the enzyme that brings about the oxidation of iodide to iodine, and it is possible that phenethylbiguanide may inhibit a reaction catalyzed by peroxidase.

The mechanism of action of DBI has not been established. However, recent studies by Wick[5] and co-workers with radioactive phenethylbiguanide (DBI) showed that this compound, when administered to rats, accumulated in the gastric juice and the liver almost to the exclusion of other tissues. These findings tend to support the previously suggested hypothesis of Wick[11] that the most important site of action of DBI is in the liver. DBI has been shown to inhibit the oxidation of succinate in vitro,[12] which could lead to an increased rate of glycolysis and lactate formation in the liver. The lactate released into the blood from this action of DBI could be readily oxidized by muscle tissue.

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REFERENCES

1. Astwood, E. B.: Mechanism of action of antithyroid compounds, Brookhaven Symposia in Biology, 7:61-73, 1954.

2. Krall, L. P., and Camerini-Davalos, R.: Early clinical evaluation of a new oral nonsulfonylurea hypoglycemic agent, Proc. of the Soc. for Exp. Biol. & Med., 95:345-347, 1957.

3. Krall, L. P., and Camerini-Davalos, R.: Clinical trials with DBI, a new nonsulfonylurea oral hypoglycemic agent, Arch. Int. Med., 102:25-31, July 1958.

4. Lambert, T. H., Bethard, W. F., Palmer, Jr., S., and Monroe, L. S.: Oral administration of Orinase (tolbutamide)—clinical observations of effect on nondiabetic and diabetic humans, Calif. Med., 88:103-108, Feb. 1958.

5. Personal communication to the author.

6. Pomeranze, J., Fujiy, H., and Mouratoff, G. T.: Clinical report of a new hypoglycemic agent, Proc. of the Soc. for Exp. Biol. & Med., 95:193, 1957.

7. Pomeranze, J.: New hypoglycemic agent, J. of Clin. Endocrin. & Metab., 17:8, 1011.

8. Tybergheim, J. M., and Williams, R. H.: Metabolic effects of phenethylbiguanide, a new hypoglycemic compound, Proc. of the Soc. for Exp. Biol. & Med., 96:1, 1957.

9. Ungar, G., Freedman, L., and Shapiro, S.: Pharmacological studies of a new oral hypoglycemic drug, Proc. of the Soc. for Exp. Biol. & Med., 95:190, 1957.

10. Williams, R. H., Tybergheim, J. M., Hyde, P. M., and Nielsen, R. L.: Studies related to the hypoglycemic action of Phenethylbiguanide, Metabolism, 6:4, 1957.

11. Wick, A. N., Larson, E. R., and Serif, G. S.: A site of action of phenethylbiguanide, a hypoglycemic compound, J. Biol. Chem., 233:296, Aug. 1958.

12. Wick, A. N., and Larson, E.: Studies with Phenethylbiguanide, Federation Proceedings, 17:334, March 1958.